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Abstract: BACKGROUND Prognosis of Takotsubo syndrome (TTS) remains controversial due to scarcity of available data. Additionally, the effect of the triggering factors remains elusive. OBJECTIVES This study compared prognosis between TTS and acute coronary syndrome (ACS) patients and investigated short- and long-term outcomes in TTS based on different triggers. METHODS Patients with TTS were enrolled from the International Takotsubo Registry. Long-term mortality of patients with TTS was compared to an age- and sex-matched cohort of patients with ACS. In addition, short- and long-term outcomes were compared between different groups according to triggering conditions. RESULTS Overall, TTS patients had a comparable long-term mortality risk with ACS patients. Of 1,613 TTS patients, an emotional trigger was detected in 485 patients (30%). Of 630 patients (39%) related to physical triggers, 98 patients (6%) had acute neurologic disorders, while in the other 532 patients (33%), physical activities, medical conditions, or procedures were the triggering conditions. The remaining 498 patients (31%) had no identifiable trigger. TTS patients related to physical stress showed higher mortality rates than ACS patients during long-term follow-up, whereas patients related to emotional stress had better outcomes compared with ACS patients. CONCLUSIONS Overall, TTS patients had long-term outcomes comparable to age- and sex-matched ACS patients. Also, we demonstrated that TTS can either be benign or a life-threating condition depending on the inciting stress factor. We propose a new classification based on triggers, which can serve as a clinical tool to predict short- and long-term outcomes of TTS. (International Takotsubo Registry [InterTAK Registry]; NCT01947621).

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Long-Term Prognosis of Patients With Takotsubo Syndrome

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ABSTRACT

BACKGROUND Prognosis of Takotsubo syndrome (TTS) remains controversial due to scarcity of available data. Additionally, the effect of the triggering factors remains elusive.

OBJECTIVES This study compared prognosis between TTS and acute coronary syndrome (ACS) patients and investigated short- and long-term outcomes in TTS based on different triggers.

METHODS Patients with TTS were enrolled from the International Takotsubo Registry. Long-term mortality of patients with TTS was compared to an age- and sex-matched cohort of patients with ACS. In addition, short- and long-term outcomes were compared between different groups according to triggering conditions.

RESULTS Overall, TTS patients had a comparable long-term mortality risk with ACS patients. Of 1,613 TTS patients, an emotional trigger was detected in 485 patients (30%). Of 630 patients (39%) related to physical triggers, 98 patients (6%) had acute neurologic disorders, while in the other 532 patients (33%), physical activities, medical conditions, or procedures were the triggering conditions. The remaining 498 patients (31%) had no identifiable trigger. TTS patients related to physical stress showed higher mortality rates than ACS patients during long-term follow-up, whereas patients related to emotional stress had better outcomes compared with ACS patients.

CONCLUSIONS Overall, TTS patients had long-term outcomes comparable to age- and sex-matched ACS patients. Also, we demonstrated that TTS can either be benign or a life-threating condition depending on the inciting stress factor. We propose a new classification based on triggers, which can serve as a clinical tool to predict short- and long-term outcomes of TTS. (International Takotsubo Registry [InterTAK Registry]; NCT01947621) (J Am Coll Cardiol 2018;72:874–82) © 2018 by the American College of Cardiology Foundation.

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Takotsubo syndrome (TTS) has been considered a relatively benign condition since its initial description in 1990 (1). Recently, we have revealed TTS as a life-threatening condition with comparable in-hospital adverse outcomes to acute coronary syndrome (ACS) (2). However, scarce data exist on long-term outcomes in patients with TTS compared with patients with ACS.

TTS can be associated with a preceding emotional or physical stressor, and approximately two-thirds of patients have identifiable triggering events (2,3). Recent data have indicated that in-hospital outcomes in TTS patients with a preceding medical illness are worse than that of patients with an emotional stressor or without an identified

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CI = confidence interval

HR = hazard ratio

TTS = Takotsubo syndrome

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stressor (4-6). However, the effect of triggering events on short- and long-term outcome has not been fully investigated. This is of particular interest, as triggering factors may significantly affect the prognosis of TTS. Physical stressors include a wide spectrum of conditions, such as neurologic conditions, pheochromocytoma, and other physical activities, medical conditions, or procedures (7,8), validating the hypothesis that patients with different physical triggers have different outcomes.

SEE PAGE 883

The aim of the present study was to compare the prognosis between TTS and ACS patients and to investigate short- and long-term outcomes in TTS according to different triggers using the database from InterTAK (International Takotsubo) Registry cohort (2,9).

METHODS

PATIENTS AND INCLUSION CRITERIA. TTS patients were included from the InterTAK Registry as previously described (2,10). Data were queried from the University Hospital Zurich and 25 collaborating hospitals in 9 countries (Austria, Finland, France, Germany, Italy, Poland, Switzerland, United Kingdom, and the United States) from January 1, 2011, to December 31, 2014. TTS was defined based on modified Mayo Clinic Diagnostic Criteria (2,11): 1) a transient wall motion abnormality in the left ventricle beyond a single epicardial coronary artery distribution; 2) the absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture, which can explain the wall motion abnormality; 3) new electrocardiographic abnormalities or elevation in cardiac troponin values; and 4) the absence of myocarditis. Patients with focal TTS matching all other criteria, in whom the wall-motion abnormality was identical to a single coronary artery territory coincidentally, were included. TTS patients who died during the acute phase before complete recovery of wall motion were not excluded. When eligibility for inclusion was unclear, cases were reviewed by core members at the University Hospital Zurich to reach an agreement. As a control group, an age- and sex-matched cohort of patients with ACS, including patients with ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, or unstable angina, was selected from the Zurich Acute Coronary Syndrome Registry. The detailed methods of ACS patient selection have already been described in our previous paper (2). Data on clinical profile and outcome were collected. This included demographics, vital signs, cardiovascular risk factors, comorbidities, laboratory values, results on electrocardiography and coronary angiography, use of medications, and use of critical care. Follow-up information of both TTS and ACS patients was obtained through telephone interviews, clinical visits, or medical records.

Patients were categorized into respective groups according to the types of preceding stressors—emotional stress, physical stress, and no identifiable trigger. In addition, physical stressors were categorized into 2 groups: 1) physical activities, medical conditions, or procedures; and 2) neurologic disorders. Patients with the combination of emotional and physical stress were excluded from the present analysis.

OUTCOMES. Long-term mortality of patients with TTS was compared with an age- and sex-matched cohort of patients with ACS. Additionally, short- and long-term outcomes including death from any cause were compared between the TTS groups based on triggers and with ACS patients.

STATISTICAL ANALYSIS. Continuous data are shown as mean ± SD, skewed variables are presented as median (interquartile range), and categorical variables are given as numbers and percentages. Comparisons of patients' characteristics between different groups were performed with 1-way analysis of variance or the Kruskal-Wallis test for continuous data and the Pearson chi-square test for categorical variables.

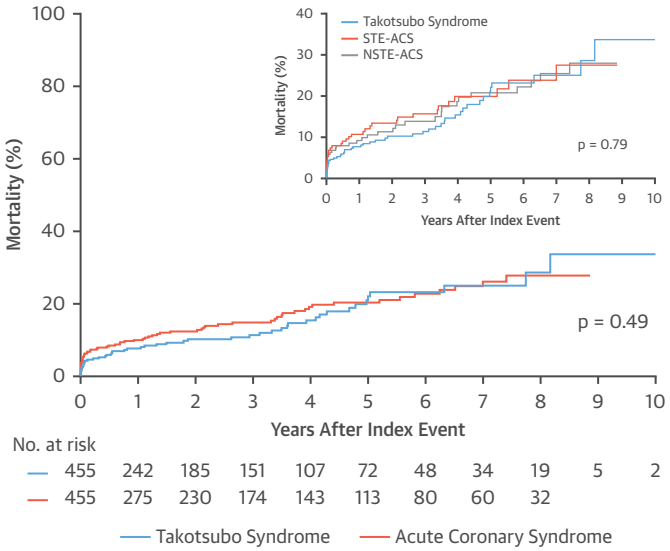
Outcome analysis was performed using Kaplan-Meier estimates and log-rank tests, as well as a landmark analysis with a landmark set at 30 days. Cox regression analysis was conducted to determine the hazard ratio (HR) and 95% confidence intervals (CIs) for long-term outcome of respective trigger factors using patients with an emotional stressor as a reference. To account for possible differences in clinical characteristics and comorbidities between different TTS groups, a multivariable adjustment analysis, including covariates that had a significant difference in the baseline comparison or were likely to have a relationship to long-term mortality, was performed in a Cox regression model. Missing data on covariates were completed with multiple imputations prior to multivariable Cox regression. An additional Cox regression analysis to obtain predictors of 30-day mortality was also performed. All tests were 2-sided, and statistical significance was defined as $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics, version 25.0 (IBM, Armonk, New York).

Graphs were compiled with Prism 7 (GraphPad, La Jolla, California).

RESULTS

COMPARISON OF TTS PATIENTS TO AGE- AND SEX-MATCHED ACS PATIENTS. Of all TTS patients in the InterTAK Registry, 455 patients were included in an analysis for the comparison to an age- and sex-matched cohort of 455 ACS patients, including 233 with ST-segment elevation ACS and 222 with non-ST-segment elevation ACS (2). Patients' characteristics and in-hospital outcomes of the TTS and age- and sex-matched cohort of ACS have already been published elsewhere (2). Long-term mortality analysis revealed similar outcomes between TTS and ACS patients ($p = 0.49$) (Figure 1).

FIGURE 1 Long-Term Mortality of Takotsubo Syndrome Compared With ACS



Kaplan-Meier curve for long-term mortality of patients with Takotsubo syndrome compared with an age- and sex-matched cohort of patients with acute coronary syndrome (ACS) including ST-segment elevation (STE) ACS (n = 233) and non–ST-segment elevation (NSTE) ACS (n = 222). Patients with Takotsubo syndrome had comparable long-term mortality risk with those with ACS ($p = 0.49$) or with STE- and NSTE-ACS ($p = 0.79$).

COMPARISON BETWEEN DIFFERENT TRIGGER GROUPS. To investigate the effects of preceding stress factors, 1,613 patients were included after the exclusion of patients whose triggering conditions could not be clearly differentiated (overlapping of emotional and physical triggers, n = 137), and categorized into respective groups based on triggers. A definite emotional stressor was detected in 485 patients (30%). Of 630 patients (39%) with a physical trigger, 98 patients (6%) were identified as having an acute neurologic disorder. The remaining patients with a physical trigger (n = 532, 33%) experienced TTS secondary to physical activities, medical conditions, or procedures. A total of 31% of TTS patients had no identifiable triggering factor (n = 498).

Main patient characteristics of all different groups are summarized in Table 1. The prevalence of women was significantly higher in TTS related to emotional stress (95%) versus physical activities, medical conditions, or procedures (85%), TTS secondary to neurologic disorders (87%), and TTS without an identifiable triggering factor (91%) ($p < 0.001$). Patients with TTS secondary to neurologic diseases were significantly younger (age 61.8 ± 14.9 years) compared with the other groups ($p < 0.001$). Laboratory analysis on admission demonstrated that troponin, creatine kinase, and brain natriuretic peptide were comparable amongst all groups. Inflammatory markers, including C-reactive protein and white blood cell count, were significantly higher in TTS secondary to physical activities, medical conditions, or procedures and TTS secondary to neurologic diseases. There was no difference in electrocardiographic findings on admission. Patients with TTS secondary to physical activities, medical conditions, or procedures and TTS secondary to neurologic diseases had higher heart rates and lower left ventricular ejection fraction on admission ($p < 0.001$ in both comparisons). Diabetes mellitus was more common in TTS secondary to physical activities, medical conditions, or procedures, while less common in TTS secondary to neurologic diseases. Cancer was more common in TTS secondary to physical activities, medical conditions, or procedures and TTS secondary to neurologic diseases. There were no significant differences in medications on admission, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, statins, and aspirin. Acute cardiac care treatment was much more common in TTS secondary to physical activities, medical conditions, or procedures (38%) and TTS secondary to neurologic diseases (50%) compared with the other groups ($p < 0.001$) (Table 1).

SHORT- AND LONG-TERM MORTALITY. Comparison of 30-day mortality between the different groups based on the triggering conditions demonstrated a substantial difference ($p < 0.001$) (Figure 2). Patients with TTS secondary to neurologic diseases had the worst prognosis, while patients with TTS related to emotional stress showed the most favorable outcome. In addition, a landmark analysis (time point set at 30 days) demonstrated a substantial difference in

TABLE 1 Clinical Characteristics of Different Triggering Groups

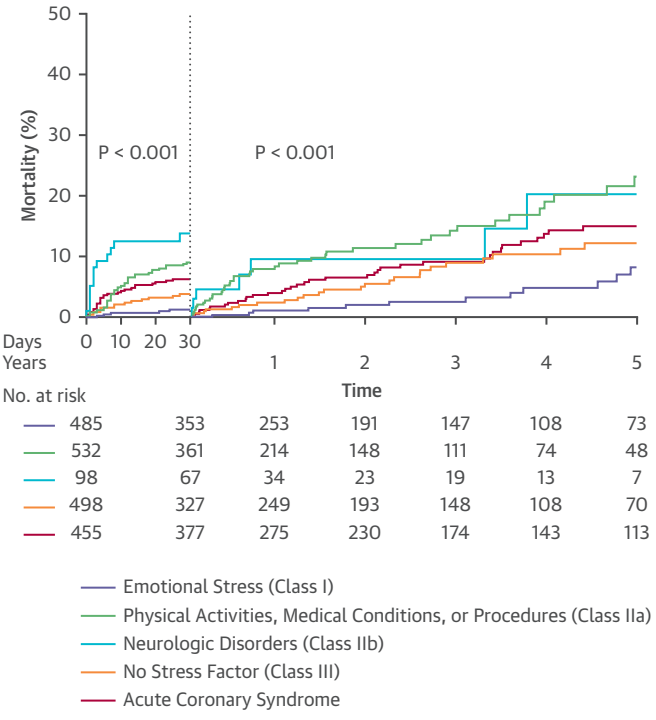
	Emotional Stress (n = 485)	Physical Activities, Medical Conditions, or Procedures (n = 532)	Neurologic Disorders (n = 98)	No Stress Factor (n = 498)	p Value
Demographics					
Female	459/485 (94.6)	454/532 (85.3)	85/98 (86.7)	452/498 (90.8)	<0.001
Age, yrs	65.4 ± 12.4 (n = 485)	66.5 ± 13.4 (n = 532)	61.8 ± 14.9 (n = 98)	68.0 ± 12.5 (n = 498)	<0.001
Takotsubo type					
Apical type	384/485 (79.2)	434/532 (81.6)	75/98 (76.5)	426/498 (85.5)	0.033
Cardiac biomarkers on admission					
Troponin, factor increase in ULN*	8.56 (3.00–21.75) n = 408	8.57 (2.60–26.00) n = 419	7.25 (2.11–38.28) n = 86	6.69 (2.00–21.72) n = 374	0.33
Creatine kinase, factor increase in ULN	0.88 (0.58–1.42) n = 346	0.83 (0.47–1.50) n = 354	0.80 (0.50–2.20) n = 60	0.78 (0.51–1.38) n = 329	0.29
BNP, factor increase in ULN†	7.24 (2.16–18.22) n = 143	5.93 (1.95–20.06) n = 140	6.52 (1.49–19.24) n = 20	6.09 (2.31–12.57) n = 102	0.87
Inflammatory markers on admission					
CRP, mg/l	3.00 (1.08–7.38) n = 348	6.40 (2.00–28.20) n = 311	5.30 (2.00–28.35) n = 54	3.10 (1.15–9.90) n = 325	<0.001
WBC, 10× 10^3/μl	9.30 (7.20–11.40) n = 403	10.45 (7.90–14.15) n = 446	11.22 (8.07–11.37) n = 90	9.35 (7.30–12.06) n = 402	<0.001
ECG on admission					
Sinus rhythm	427/455 (93.8)	423/470 (90.0)	72/78 (92.3)	417/453 (92.1)	0.20
ST-segment elevation	204/455 (44.8)	181/470 (38.5)	34/77 (44.2)	214/450 (47.6)	0.44
ST-segment depression	27/455 (5.9)	42/470 (8.9)	7/77 (9.1)	31/450 (6.9)	0.31
T-wave inversion	185/455 (40.7)	199/470 (42.3)	25/77 (32.5)	184/450 (40.9)	0.44
QTc, ms	458.7 ± 44.9 (n = 334)	454.9 ± 52.1 (n = 367)	465.3 ± 60.3 (n = 64)	456.8 ± 49.8 (n = 293)	0.43
Hemodynamics					
Heart rate, beats/min	85.4 ± 19.2 (n = 416)	91.5 ± 24.0 (n = 425)	92.2 ± 26.9 (n = 79)	85.4 ± 21.2 (n = 410)	<0.001
Systolic blood pressure, mm Hg	130.8 ± 27.2 (n = 421)	127.3 ± 30.6 (n = 421)	134.6 ± 33.4 (n = 81)	132.8 ± 26.6 (n = 408)	0.021
Left ventricular ejection fraction, %‡	42.5 ± 10.9 (n = 452)	39.0 ± 12.2 (n = 492)	37.7 ± 12.9 (n = 90)	42.3 ± 11.7 (n = 437)	<0.001
Cardiovascular risk factors/history					
Hypertension	293/478 (61.3)	348/518 (67.2)	54/91 (59.3)	327/477 (68.6)	0.049
Diabetes mellitus	50/476 (10.5)	99/519 (19.1)	6/91 (6.6)	64/481 (13.3)	<0.001
Current smoking	85/471 (18.0)	107/505 (21.2)	24/91 (26.4)	79/459 (17.2)	0.15
Hypercholesterolemia	154/478 (32.2)	159/516 (30.8)	27/90 (30.0)	165/478 (34.5)	0.61
Comorbidities					
Cancer	48/453 (10.6)	108/497 (21.7)	20/88 (22.7)	65/441 (14.7)	<0.001
Psychiatric disorders§	150/396 (37.9)	162/496 (32.7)	32/90 (35.6)	84/413 (20.3)	<0.001
Medication on admission					
ACE inhibitor or ARB	158/415 (38.1)	148/422 (35.1)	27/73 (37.0)	154/375 (41.1)	0.38
Beta-blocker	143/415 (34.5)	128/422 (30.3)	20/73 (27.4)	133/375 (35.5)	0.28
Statin	73/403 (18.1)	79/417 (18.9)	11/73 (15.1)	62/362 (17.1)	0.83
Aspirin	141/403 (35.0)	122/417 (29.3)	21/73 (28.8)	132/362 (36.5)	0.17
In-hospital complications	20/479 (4.2)	111/524 (21.2)	23/98 (23.5)	40/483 (8.3)	<0.001
Cardiogenic shock	17/479 (3.5)	94/523 (18.0)	13/98 (13.3)	36/483 (7.5)	<0.001
Death	5/485 (1.0)	37/532 (7.0)	13/98 (13.3)	14/498 (2.8)	<0.001
Acute cardiac care treatment	38/484 (7.9)	199/527 (37.8)	49/98 (50.0)	47/489 (9.6)	<0.001
Intra-aortic balloon pump	7/484 (1.4)	21/527 (4.0)	2/98 (2.0)	11/489 (2.2)	0.07
Invasive or noninvasive ventilation	21/484 (4.3)	174/527 (33.0)	45/98 (45.9)	39/489 (8.0)	<0.001
Cardiopulmonary resuscitation	16/484 (3.3)	73/527 (13.9)	16/98 (16.3)	33/489 (6.7)	<0.001
Catecholamine use	24/484 (5.0)	116/527 (22.0)	28/98 (28.6)	31/489 (6.3)	<0.001

Values are n/N (%) mean ± SD, or median (interquartile range). *Including upper limits of the normal range for troponin T, high-sensitivity troponin T, and troponin I. †Including upper limits of the normal range for brain natriuretic peptide and the N-terminal of prohormone brain natriuretic peptide. ‡Data obtained during catheterization or echocardiography; if both results were available, data from catheterization were used. §Patients could have an acute disorder as well as past or chronic disorder.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BNP = brain natriuretic peptide; CRP = C-reactive protein; ECG = electrocardiogram; QTc = QT interval corrected for heart rate; ULN = upper limit of the normal; WBC = white blood cell count.

long-term mortality between the different groups ($p < 0.001$) (Figure 2). Whereas patients with TTS secondary to neurologic diseases and TTS secondary to physical activities, medical conditions, or procedures had a less favorable long-term outcome than ACS, patients with TTS related to emotional stress had more favorable prognosis compared with ACS. Preceding physical activities, medical conditions, or procedures (HR: 3.78; 95% CI: 2.21 to 6.44; $p < 0.001$), neurologic disorders (HR: 5.76; 95% CI: 2.96 to 11.2; $p < 0.001$), and no identifiable trigger (HR: 2.14; 95% CI: 1.20 to 3.82; $p = 0.010$) emerged as strong independent risk factors for 5-year mortality when using preceding emotional stressors as the reference group (Figure 3). In an additional Cox regression analysis, preceding physical activities, medical conditions, or procedures; neurologic disorders; and no identifiable trigger were also identified as independent predictors of 30-day mortality (Online Figure 1).

FIGURE 2 Short- and Long-Term Mortality of Different Triggering Groups



Kaplan-Meier survival curve of different triggering groups and acute coronary syndrome as a reference group with landmark analysis at 30 days. Comparison of 30-day mortality between the different groups based on the triggering conditions demonstrated a substantial difference ($p < 0.001$). After 30 days, a substantial difference in long-term mortality (5 years) between the different groups still exists ($p < 0.001$). Patients with acute coronary syndrome showed intermediate short- and long-term mortality between patients with emotional and physical TTS triggering groups. TTS = Takotsubo syndrome.

DISCUSSION

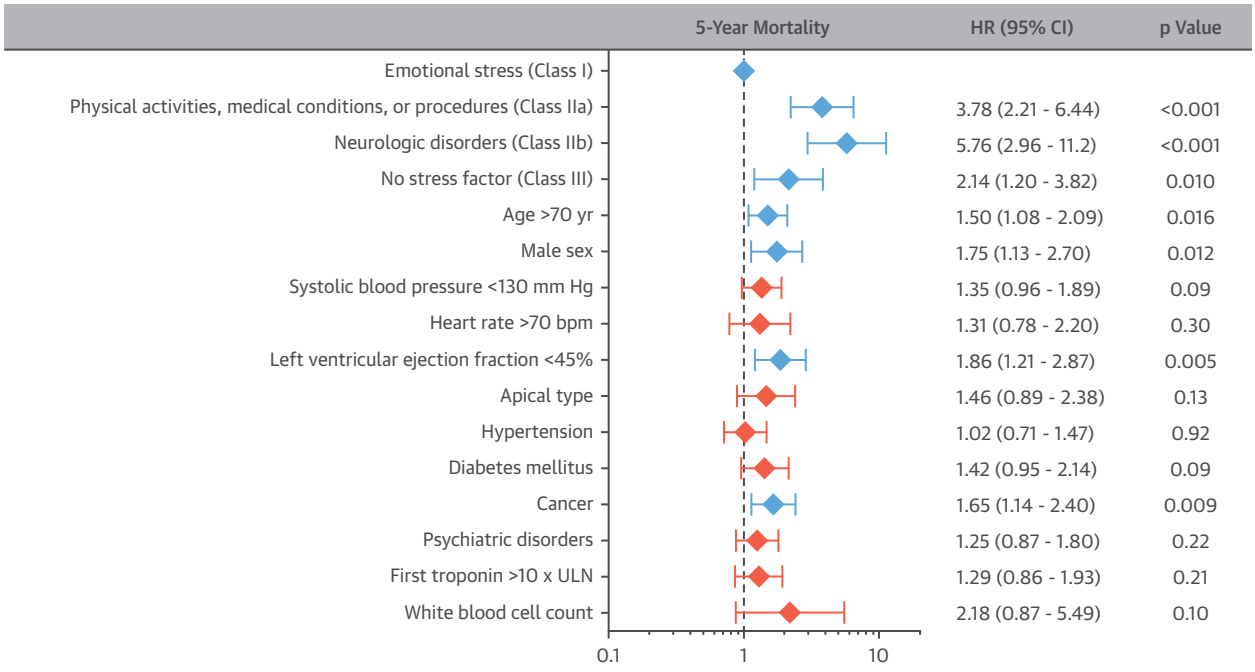
The principal findings of the present study were as follows: 1) overall, TTS patients had a similar long-term outcome compared with age- and sex-matched ACS patients; 2) TTS patients with events related to emotional stress had a favorable short- and long-term prognosis; 3) TTS secondary to neurologic diseases had the worst short-term prognosis; and 4) TTS secondary to neurologic diseases and TTS secondary to physical activities, medical conditions, or procedures had significantly higher mortality rates compared with ACS during long-term follow-up.

Recently, we have reported that in-hospital mortality of TTS is similar to that of ACS (2). However, scarce data exist on long-term outcomes in patients with TTS compared with patients with myocardial infarction (12–14). Additionally, these studies (13,15) are limited by the fact that they only include patients with ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction as a comparison group without considering patients with unstable angina, which is important as TTS patients can also present with signs and symptoms of unstable angina and without any notable electrocardiographic abnormalities. Second, these studies have had inconsistent results regarding patient outcomes, with some showing equal mortality rate to ACS, and some showing increased mortality in patients with TTS (12,13,15).

TTS is typically triggered by a preceding emotional or physical stressor, and approximately two-thirds of patients have identifiable triggering events (2,3,16,17). We have recently shown that physical triggers are an independent predictor of a worse in-hospital outcome (2). However, triggering conditions, especially physical triggers of TTS, vary substantially, ranging from critical conditions such as a septic shock treated in the intensive care unit to harmless conditions including vigorous housework (7,18). Therefore, we hypothesized that patients with different physical triggers have different short- and long-term outcomes.

Of note, TTS patients with an emotional stressor more often had typical features of TTS, such as female sex and chest pain, compared with patients in other groups. Interestingly, patients with TTS secondary to a neurologic disorder were significantly younger than TTS patients of other groups. These epidemiological differences might reflect the biological background. Patients with TTS secondary to physical activities, medical conditions, or procedures and those with TTS secondary to neurologic disorders showed higher

FIGURE 3 Outcome Predictors



Multiple Cox regression to adjust for potential confounders for long-term mortality. Preceding physical activities, medical conditions, or procedures; neurologic disorders; and no identifiable trigger were identified as strong independent risk factors for 5-year mortality using preceding emotional stressors as the reference group. In addition, age >70 years, male sex, left ventricular ejection fraction <45%, and cancer emerged as independent predictors. **Blue** indicates statistically significant predictors, **orange** not significant. bpm = beats/min; CI = confidence interval; HR = hazard ratio; ULN = upper limit of the normal range.

heart rates compared with those with emotional triggers. This observation might suggest that the degree of catecholamine surge was more severe in patients with physical or neurologic triggers than in those with emotional triggers. Furthermore, it is likely that higher catecholamine levels can increase the risk of developing cardiogenic shock via pump failure due to large ballooning area and/or left ventricular outflow tract obstruction due to hypercontractility of the basal segment (19). In addition, inflammatory markers such as C-reactive protein and white blood cell count were also higher in patients with physical or neurologic disorders. Thus, it is conceivable that a synergistic effect of a severe cardiac dysfunction and enhanced inflammatory response leads to a poor hemodynamic status, which in turn causes an unfavorable short-term outcome.

According to the triggering conditions, TTS patients with events secondary to neurologic disorders had the highest mortality; this is also in line with a recently published work showing that neurologic diseases are associated with an unfavorable outcome (10). This is not surprising, as the prognosis of these patients is likely to be affected by the underlying disease. In other words, the increased mortality in patients with neurologic triggers may be engendered by the combined risk of TTS plus the intrinsic risk of any precipitating comorbidity, such as cerebrovascular hemorrhage. Patients with TTS secondary to physical activities, medical conditions, or procedures had the second worst prognosis at 30-day follow-up. However, TTS secondary to neurologic disorders and TTS secondary to physical activities, medical conditions, or procedures showed almost similar unfavorable outcomes at 5 years after the TTS index event; indeed, neurologic diseases mostly drive patient outcome during the acute phase. As the mortality rate of TTS secondary to physical activities, medical conditions, or procedures increases to that of TTS secondary to neurologic disease at 5-year follow-up, this may be explained by a higher prevalence of chronic coexisting morbidities such as diabetes mellitus in patients with TTS secondary to physical activities, medical conditions, or procedures compared with those with TTS secondary to neurologic diseases.

CENTRAL ILLUSTRATION **InterTAK Classification**

Class I:	Takotsubo syndrome related to emotional stress
Class II:	Takotsubo syndrome related to physical stress
Class IIa:	Takotsubo syndrome secondary to physical activities, medical conditions, or procedures
Class IIb:	Takotsubo syndrome secondary to neurologic disorders
Class III:	Takotsubo syndrome without an identifiable triggering factor

Ghadri, J.R. et al. J Am Coll Cardiol. 2018;72(8):874–82.

Novel classification proposed, based on the type of triggering event.

Singh et al. (20) conducted a meta-analysis, which reported that TTS patients with underlying noncardiac conditions showed higher in-hospital mortality rate compared with those without. Of note, our study demonstrates different short- and long-term outcomes of TTS patients with diverse physical triggers. Additionally, TTS patients with an emotional stressor showed a favorable short- and long-term outcome compared with those with a physical stressor or ACS patients. Therefore, TTS is a much more complex syndrome than previously thought, and should be classified according to the underlying trigger event to accurately risk stratify and predict short- and long-term outcomes for individual patients. Thus, we propose a new classification according to results of the present study (**Central Illustration**). This new classification (InterTAK Classification) could be useful to predict short- and long-term outcomes of TTS patients.

STUDY LIMITATIONS. This is a registry of an observational nature. Therefore, invisible confounders cannot be excluded. Patients with physical activity were classified as Class IIa and not as a single category due to the small sample size.

CONCLUSIONS

It was assumed for quite a long time that TTS is a benign condition; however, it has recently been shown that TTS is a life-threatening illness with substantial morbidity and mortality in the acute phase and outcomes similar to that of ACS. Given the heterogenous character of triggers, TTS encompasses a wide spectrum ranging from a benign to fatal condition. As such, TTS is much more multifaceted than suggested. The old woman with an emotional triggering event and apical ballooning, "the classic TTS patient," indeed has a good short- and long-term prognosis, whereas patients with TTS secondary to neurologic disorders and TTS secondary to physical activities, medical conditions, or procedures reveal an unfavorable outcome. As medicine approaches delivery of personalized medicine and our knowledge about TTS grows, it is crucial to consider the "individual patient" to perhaps improve prognosis. Thus, the new InterTAK Classification based on the type of triggering event might be a useful clinical tool for risk stratification.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The long-term outcome of patients with TTS is highly variable. The prognosis is more favorable when the syndrome is triggered by emotional events than when it develops in response to physical or neurologic conditions.

TRANSLATIONAL OUTLOOK: Further investigation of the relationships between the triggering provocative circumstances could help elucidate the pathophysiological mechanisms responsible for this acute cardiac condition.

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KEY WORDS acute coronary syndrome, broken heart syndrome, classification, outcome, stress factor, Takotsubo syndrome

APPENDIX For a supplemental figure, please see the online version of this paper.